SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Perizam 2mg/ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 2mg Clobazam
Excipient(s) with known effect:
Sodium Methyl parahydroxybenzoate (E219) (1.32mg)
Sodium Propyl parahydroxybenzoate (E217) (0.33mg)
Liquid Maltitol (E965) (0.3g)
Propylene Glycol (E1520) (6.21mg)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral Suspension

An off-white suspension.

4.1 Therapeutic indications

Perizam is a 1,5-benzodiazepine indicated in adults for the short-term symptomatic treatment (2-4 weeks, maximum 4 weeks including tapering off period) only of anxiety that is severe, disabling or subjecting the individual to unacceptable distress.

In treatment of anxiety states associated with affective disorders, perizam must only be used in conjunction with adequate treatments for the underlying disorder.

In patients with schizophrenic or other psychotic illnesses, use of benzodiazepines is recommended only for short term symptomatic

management of hyperarousal and agitation. Benzodiazepines do not possess antipsychotic properties.

Perizam may be used as adjunctive therapy in epilepsy in adults or children over 2 years, if standard treatment with one or more anticonvulsants has failed: Treatment of simple or complex partial epilepsy with or without secondary generalisation and treatment of all types of generalised epilepsy (tonic/clonic, myoclonic, absence seizures).

4.2 Posology and method of administration

Prior to starting treatment with Perizam, a discussion should be held with patients to put in place a strategy for ending treatment with Perizam in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

Treatment should be given for the shortest possible duration. If this medicine is being used for the treatment of epilepsy this medicine should be used for as long as the prescriber considers it necessary.

Posology

If low doses are required, the 1mg/ml strength product the most suitable presentation. If high doses are required, the 2mg/ml strength product is the most suitable presentation.

Treatment of anxiety

Adults

The usual anxiolytic dose for adults is 20-30 mg daily in divided doses or as a single dose given at night. Doses up to 60mg daily have been used in the treatment of adult in-patients with severe anxiety.

The lowest dose that can control symptoms should be used. After improvement of the symptoms, the dose may be reduced.

It should not be used for longer than 4 weeks (including the tapering off period). Long term chronic use as an anxiolytic is not recommended. In certain cases, extension beyond the maximum treatment period may be necessary; treatment must not be extended without re-evaluation of the patient's status using special expertise. It is strongly recommended that prolonged periods of uninterrupted treatment be avoided, since they may lead to dependence. Treatment should always be withdrawn gradually. Patients who have taken Perizam for a long time may require a longer period during which doses are reduced.

Elderly:

Doses of 10-20 mg daily in anxiety may be used in the elderly, who are more sensitive to the effects of psychoactive agents. Treatment requires low initial doses and gradual dose increments under careful observation.

Treatment of epilepsy in association with one or more other anticonvulsants

Adults

In epilepsy a starting dose of 20-30 mg/day is recommended, increasing as necessary up to a maximum of 60 mg daily.

Elderly

Treatment requires low initial doses and gradual dose increments under careful observation.

Paediatric patients over 2 years:

Perizam doses should be adapted individually. Doses can be taken once a day or divided in 2 – 3 times a day, keeping the same total dose.
The patient must be re-assessed after a period not exceeding 4 weeks and every 4 weeks thereafter in order to evaluate the need for continued treatment. A break in therapy may be beneficial if drug exhaustion develops, recommencing therapy at a low dose. At the end of treatment (including in poor-responding patients), since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended to gradually decrease the dosage.

When prescribed for children treatment requires low initial doses and gradual dose increments under careful observation. Clobazam is typically initiated at a low dose, often 5 mg/day or 0.1 mg/kg/day for younger patients, and increased by step of 0.1 to 0.2 mg/kg/day at 7 days intervals, until a minimum effective dose is reached or side effects occur. Studies have suggested that slow titration may help avoid adverse effects and that when present, side effects may be reduced or eliminated with dose reduction.
The following up-titration regimen has been proposed in the literature in order to take into account the high metabolism variability linked to the P450 system maturation - especially in the presence of inducers and inhibitors - and should be used with increase of the dose by 0.1 to 0.2 mg/kg every week up to the targeted dose.

A maintenance dose of 0.3 to 1mg/kg body weight daily is usually sufficient.

The oral suspension is particularly recommended for children and adults with swallowing difficulties, as it allows a secure and precise dosage.

Perizam should not be used as an anticonvulsivant treatment in children from 6 months to 2 years old, unless under exceptional situations, when there is a clear epilepsy indication. The starting dose in this exceptional circumstances should be the lowest one (0.1 mg/kg/day) and titration should be even more cautious, not more than 0.1 mg/kg/day as in this population the metabolic pathways for clobazam may not be fully mature. Up-to-date, no precise dosage recommendation can be made in this population.

Hepatic and renal failure

Treatment requires low initial doses and gradual dose increments under careful observation regardless of the age group of the patient.

Method of administration

For oral use only

Once titrated to an effective dose of Clobazam, patients should remain on their treatment and care should be exercised when changing between different formulations. (See section 4.4-Switching between formulations)

This product may settle during storage. Please shake the bottle thoroughly before use.

Perizam can be taken with or without food.

4.3 Contraindications

Perizam must not be used:

− In patients with hypersensitivity to benzodiazepines or any of the excipients of Perizam.

− In patients with any history of drug or alcohol dependence (increased risk of development of dependence).

− In patients with myasthenia gravis (risk of aggravation of muscle weakness).

− In patients with severe respiratory insufficiency (risk of deterioration).

− In patients with sleep apnoea syndrome (risk of deterioration).

− In patients with severe hepatic insufficiencies (risk of precipitating encephalopathy).

- During the first trimester of pregnancy (for use during the second and third trimester, see section 4.6).

− In breast-feeding women.

- Acute intoxication with alcohol and CNS-active substances.

Benzodiazepines must not be given to children without careful assessment of the need for their use.

Perizam should not be used in children from 6 months to 2 years old, unless under exceptional situations as an anti-convulsivant treatment, when there is a clear epilepsy indication.

4.4 Special warnings and precautions for use

Before treatment of anxiety states associated with emotional instability, it must first be determined whether the patient suffers from a depressive disorder requiring adjunctive or different treatment. Indeed, in patients with anxiety associated with depression, Perizam must be used only in conjunction with adequate concomitant treatment. Use of benzodiazepine (such as Perizam) alone, can precipitate suicide in such patients.

Switching between formulations

In some individuals taking Perizam, the drug reaches higher plasma levels than the same dose taken as a tablet. This may lead to an increased risk of respiratory depression and sedation which may be most noticeable when switching to this medicine from tablets. Therefore, caution must be taken when switching between clobazam products as the mean Cmax on single dose administration for the suspension is higher than that observed for the tablet formulation.

Children

There is a lack of data regarding the use of the product in patients under 2 years old. For this reason, careful assessment and monitoring is required by the treating physician for use in children under 2 years for anticonvulsant treatment.

- **Alcohol**

It is recommended that patients abstain from drinking alcohol during treatment with clobazam (increased risk of sedation and other adverse effects (please refer to section 4.5 Interactions with other Medicinal Products and other forms of Interaction)).
Benzodiazepines including clobazam, should be used with extreme caution in patients with a history of alcohol or drug abuse.

- **Risks from concomitant use of opioids and benzodiazepines:**

Concomitant use of Perizam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as

Perizam with opioids should be reserved for patients for whom alternative treatment options are not possible.

If a decision is made to prescribe Perizam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their environment to be aware of these symptoms (see section 4.5).

- **Drug dependence, tolerance and potential for abuse**

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with Perizam should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

- **Drug withdrawal syndrome**

Prior to starting treatment with Perizam, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with Perizam should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care and for use in epilepsy).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.
If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

- **Amnesia**

Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also Undesirable Effects). In case of loss or bereavement psychological adjustment may be inhibited by benzodiazepines.

- **Psychiatric and 'paradoxical' reactions**

They are more likely to occur in children and the elderly.
Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse

behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the drug should be discontinued.

- **Elderly patients**

In the elderly, due to the increased sensitivity to adverse reactions such as drowsiness, dizziness, muscle weakness, there is an increased risk of fall that may result in serious injury. A dose reduction is recommended.

- **Serious Skin Reactions**

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported with clobazam in both children and adults during the post-marketing experience. A majority of the reported cases involved the concomitant use of other drugs, including antiepileptic drugs, that are associated with serious skin reactions.
SJS/TEN could be associated with a fatal outcome. Patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment. Clobazam should be immediately discontinued when SJS/TEN is suspected. If signs or symptoms suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered (see Section 4.8)

- **Respiratory Depression**

Respiratory function should be monitored in patients with chronic or acute severe respiratory insufficiency and a dose reduction of clobazam may be necessary. Clobazam is contraindicated in patients with severe respiratory insufficiency (please refer to section 4.3 Contraindications).

- **Renal and hepatic impairment**

In patients with impairment of renal or hepatic function, responsiveness to clobazam and susceptibility to adverse effects are increased, and a dose reduction may be necessary. In long term treatment renal and hepatic function must be checked regularly. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

- **Muscle weakness**

Clobazam may cause muscle weakness, therefore, in patients with pre-existing muscle weakness or spinal or cerebellar ataxia or sleep apnoea, special observation is required and a dose reduction may be necessary. Clobazam is contraindicated in patients with myasthenia gravis.

- **Suicidal ideation, suicide attempt, suicide and depression**

Some epidemiological studies suggest an increased incidence of suicidal ideation, suicide attempt and suicide in patients with or without depression and treated with benzodiazepines and other hypnotics, including clobazam. However, a causal relationship has not been established (see section 4.8).

- **Personality disorders**

Disinhibiting effects may be manifested in various ways. Suicide may be precipitated in patients who are depressed and aggressive behaviour towards self and others may be precipitated. Extreme caution should therefore be used in prescribing benzodiazepines in patients with personality disorders

- **CYP2C19 poor metabolizers**

In patients who are CYP2C19 poor metabolisers, levels of the active metabolite N-desmethylclobazam are expected to be increased as compared to extensive metabolizers. Dosage adjustment of clobazam may be necessary (e.g. low starting dose with care dose titration (please refer to section 5.2)).

- **Concomitant use of cannabidiol**

The concomitant use of clobazam with cannabidiol-containing medicinal and non-medicinal products may result in increased exposure to N-desmethylclobazam, leading to increased incidence of somnolence and sedation. Dosage adjustment of clobazam may be necessary. Non-medicinal products containing cannabidiol must not be taken in combination with clobazam as they contain unknown quantities of cannabidiol and are of variable quality (see sections 4.5 and 5.2).

Excipient Warnings

- Perizam contains 2.3 mg of sodium per ml, equivalent to 0.12% of the WHO recommended maximum daily intake of 2g sodium for an adult. This should be taken into account by patients on a low sodium diet.
- Sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate. These may cause an allergic reaction. This allergy may happen some time after starting the medicine.
- Liquid Maltitol (E965) 0.3g in 1 ml. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
- Propylene Glycol (E1520) 6.21mg in 1ml. Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates.

4.5 Interaction with other medicinal products and other forms of interaction

- **Alcohol**

Concomitant consumption of alcohol can increase the bioavailability of clobazam by 50% (please refer to Section 5.2) and therefore increase the effects of clobazam e.g. sedation (please refer to section 4.5).

Central nervous system depressant drugs

Especially when clobazam is administered at higher doses, an enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anticonvulsant drugs, anaesthetics and sedative antihistamines. Special caution is also necessary when clobazam is administered in cases of intoxication with such substances or with lithium.

- **Opioids**

The concomitant use of benzodiazepines, including clobazam, and opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. Limit dosage and duration of concomitant use of benzodiazepines and opioids (see section 4.4).

- **Anticonvulsants**

Addition of clobazam to established anticonvulsant medication (eg, phenytoin, valproic acid) may cause a change in plasma levels of these drugs. If used as an adjuvant in epilepsy the dosage of Perizam should be determined by monitoring the EEG and the plasma levels of the other drugs checked.

Phenytoin and carbamazepine may cause an increase in the metabolic conversion of clobazam to the active metabolite N-desmethyl clobazam.

Stiripentol increases plasma levels of clobazam and its active metabolite N-desmethylclobazam, through inhibition of CYP3A and CYP2C19. Monitoring of blood levels of clobazam and active metabolite is recommended, prior to initiation of stiripentol, and then once new steady-state concentration has been reached, i.e. after 2 weeks approximately. Clinical monitoring is recommended and dose adjustment may be necessary.

- **MAOIs**

Concomitant administration of drugs, inhibit the monooxygenase system, such as cimetidine and erythromycin, can enhance the effects of Clobazam.

- **Narcotic analgesics**

If clobazam is used concomitantly with narcotic analgesics, possible euphoria may be enhanced; this may lead to increased psychological dependence.

- **Muscle relaxants**

The effects of muscle relaxants, analgesics and nitrous oxide may be enhanced.

- **CYP 2C19 inhibitors**

Strong and moderate inhibitors of CYP2C19 may result in increased exposure to N-desmethylclobazam (N-CLB), the active metabolite of clobazam. Dosage adjustment of clobazam may be necessary when co-administered with strong (e.g. fluconazole, fluvoxamine, ticlopidine) or moderate (e.g. omeprazole) CYP2C19 inhibitors (please refer to Section 5.2).

- **Cannabidiol**

When cannabidiol and clobazam are co-administered, bi-directional PK interactions occur. Based on a healthy volunteer study, elevated levels (3- to 4-fold) of N-desmethylclobazam (an active metabolite of clobazam) can occur when combined with cannabidiol, likely mediated by CYP2C19 inhibition. Increased systemic levels of these active substances may lead to enhanced pharmacological effects and to an increase in adverse drug reactions. Concomitant use of cannabidiol and clobazam increases the incidence of somnolence and sedation. Reduction in dose of clobazam should be considered if somnolence or sedation are experienced when clobazam is co-administered with cannabidiol.

- **CYP 2D6 substrates**

Clobazam is a weak CYP2D6 inhibitor. Dose adjustment of drugs metabolized by CYP2D6 (e.g. dextromethorphan, pimozide, paroxetine, nebivolol may be necessary.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of clobazam in pregnant women. Nevertheless, a large amount of data collected from cohort studies has not demonstrated evidence of the occurrence of major malformations following exposure to benzodiazepines during the first trimester of pregnancy, although incidence of cleft lip and palate were observed in case-control studies.

Clobazam is not recommended during pregnancy and in women of childbearing potential not using contraception.

Clobazam crosses the placenta. Animal studies have demonstrated reproductive toxicity (see section 5.3).

Women of childbearing potential should be informed of the risks and benefits of the use of clobazam during pregnancy.

Women of childbearing potential should be informed to contact her physician regarding discontinuation of the product if they are pregnant or intend to become pregnant. If clobazam treatment is to be continued, use clobazam at the lowest effective dose.

Cases of reduced fetal movement and fetal heart rate variability have been described after administration of benzodiazepines during the second and/or third trimester of pregnancy.

Administration of clobazam before or during childbirth can result in the occurrence of respiratory depression (including respiratory distress and apnea), which may be associated with other disorders such as sedation signs, hypothermia, hypotonia, and feeding difficulties in the new born (signs and symptoms of the so-called “floppy infant syndrome”).

Moreover, infants born to mothers who have taken benzodiazepines over longer periods during the later stages of pregnancy may have developed physical dependence and may be at risk for developing withdrawal symptoms in the postnatal period. Appropriate monitoring of the newborn in the postnatal period is recommended.

Breast-feeding

Since benzodizepines are found in the breast milk, clobazam must not be used in breast-feeding women.

Fertility
There is insufficient information to assess effects of clobazam on fertility in humans. In a fertility study in male and female rats no effect on fertility was observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Clobazam has major influence on the ability to drive and use machines. Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also Interactions).

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive.

• Do not drive until you know how the medicine affects you.

• It is an offence to drive while under the influence of this medicine.

• However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1,000 to ≤1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).

Metabolism and nutrition disorders

Common: decreased appetite

Psychiatric disorders

Common: irritability, aggression, restlessness, depression (pre-existing depression may be unmasked), drug tolerance (especially during prolonged use) (see section 4.4), agitation

Uncommon: abnormal behavior, confusional state, anxiety, delusion,

nightmare, loss of libido (particularly with high doses or in long-term

treatment, and is reversible)

Not known: drug dependence (see section 4.4), initial insomnia, anger, hallucination, psychotic disorder, poor sleep quality, suicidal ideation

Nervous system disorders

Very common: somnolence, especially at the beginning of treatment and when higher doses are used

Common: sedation, dizziness, disturbance in attention, slow speech/dysarthria/speech disorder (particularly with high doses or in long-term treatment, and is reversible), headache, tremor, ataxia

Uncommon: emotional poverty, amnesia (may be associated with abnormal behaviour), memory impairment, anterograde amnesia (in the normal dose range, but especially at higher dose levels)

Not known: cognitive disorder, altered state of consciousness (particularly in elderly patients, may be combined with respiratory disorders), nystagmus (particularly with high doses or in long-term treatment), gait disturbance (particularly with high doses or in long-term treatment, and is reversible).

Eye disorders

Uncommon: diplopia (particularly with high doses or in long-term treatment, and is reversible)

Respiratory, thoracic and mediastinal disorders

Not known: respiratory depression, respiratory failure particularly in patients with pre-existing compromised respiratory function e.g. in patients with bronchial asthma or brain damage) (see section 4.3 and 4.4)

Gastrointestinal disorders

Common: dry mouth, nausea, constipation

Skin and subcutaneous tissue disorders

Uncommon: rash

Not known: photosensitivity reaction, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis (including some cases with fatal outcome)

Musculoskeletal and connective tissue disorders

Not known: muscle spasms, muscle weakness

General disorders and administration site conditions

Very common: fatigue, especially at the beginning of treatment and when higher doses are used

Not known: slow response to stimuli, hypothermia, drug withdrawal symptoms (see 4.4 Special warnings and precautions)*.

*Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of "rebound" phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.

In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the

extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

Investigations

Uncommon: weight increased (particularly with high doses or in long-term treatment, and is reversible)

Injury, poisoning and procedural complications

Uncommon: fall

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continuing monitoring of the benefit/ risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death. As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol).

In the management of overdose, it is recommended that the possible involvement of multiple agents be taken into consideration.

Following overdose with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious, or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in

emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

Secondary elimination of clobazam (by forced diuresis or haemodialysis) is ineffective.

Consideration should be given to the use of flumazenil as a benzodiazepine antagonist.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Anxiolytics

ATC code: N05BA09

Clobazam is a 1,5-benzodiazepine and the pharmacodynamic activity is qualitatively similar to that of other compounds of this class:

- Muscle relaxant
- Anxiolytic
- Sedative
- Hypnotic
- Anticonvulsant
- Amnesic.

These effects are related to a specific agonist action upon a central part of the receptor complex 'Gaba-Omega' macromolecular receptors'. Also known as BZ1 and BZ2 and modulating the opening of the chloride channel.

In single doses up to 20mg or in divided doses up to 30mg, clobazam does not affect psychomotor function, skilled performance, memory or higher mental functions.

5.2 Pharmacokinetic properties

• Absorption

After oral administration, clobazam is rapidly and extensively absorbed.

Time to peak plasma concentrations (Tmax) is achieved from 0.5 – 4.0 hrs.

The peak plasma level of clobazam after oral administration of Clobazam Oral Suspension 2mg/ml was higher than that observed after administration of a reference 10mg tablet in a single dose, randomised, crossover bioequivalence study (mean Cmax 263.1 ± 54.38 ng and 224.00 ± 22.96 ng/ml, respectively).

Concomitant intake of alcohol can increase the bioavailability of clobazam by 50%.

• Distribution

After a single dose of 20 mg clobazam, marked interindividual variability in maximum plasma concentrations (222 to 709 ng/ml) was observed after 0.25 to 4 hours. Clobazam is lipophilic and distributes rapidly throughout the body. Based on a population pharmacokinetic analysis, the apparent volume of distribution at steady-state was approximately 102 L, and is concentration independent over the therapeutic range. Approximately 80 – 90% of clobazam is bound to plasma protein.

Clobazam accumulates approximately 2-3 fold to steady-state while the active metabolite N-desmethylclobazam (N-CLB) accumulates approximately 20-fold following clobazam twice daily administration. Steady state concentrations are reached within approximately 2 weeks.

• Metabolism

Clobazam is rapidly and extensively metabolized in the liver. Clobazam metabolism occurs primarily by hepatic demethylation to N-desmethylclobazam (N-CLB), mediated by CYP3A4 and to a lesser extent by CYP2C19. N-CLB is an active metabolite and the main circulating metabolite found in human plasma.

N-CLB undergoes further biotransformation in the liver to form 4-hydroxy-N-desmethylclobazam, primarily mediated by CYP2C19.

CYP2C19 poor metabolizers exhibit a 5-fold higher plasma concentration of N-CLB compared to extensive metabolizers.

Clobazam is a weak CYP2D6 inhibitor. Co-administration with dextromethorphan led to increases of 90% in AUC and 59% in Cmax values for dextromethorphan.

Concomitant administration of 400 mg ketoconazole (CYP3A4 inhibitor) increased Clobazam AUC by 54% with no effect on Cmax. These changes are not considered clinically relevant.

• Elimination

Based on a population pharmacokinetic analysis, plasma elimination half-lives of clobazam and N-CLB were estimated to be 36 hours and 79 hours respectively.

Clobazam is cleared mainly by hepatic metabolism with subsequent renal elimination. In a mass balance study, approximately 80% of the administered dose was recovered in urine and about 11% in the faeces. Less than 1 % of unchanged clobazam and less than 10% of unchanged N-CLB are excreted through the kidneys.

- **Populations at Risk**

Elderly

Hepatic metabolism decreases and total clearance with increasing concentrations at equilibrium, the free-fraction and half-lives. It is important to reduce the dose.

Hepatic Impairment

There is a decrease in total clearance.

5.3 Preclinical safety data

Teratogenicity
Oral administration of clobazam to pregnant rats and rabbits throughout the period of organogenesis resulted in increased embryofetal mortality and increased incidences of fetal skeletal variations. In rabbits clobazam also decreased fetal bodyweights and increased the incidence of fetal malformations (visceral and skeletal). Additionally, oral administration of clobazam to rats throughout pregnancy and lactation resulted in decreased pup survival and alterations in offspring behaviour (locomotor activity). The observed embryo-fetal effects were associated with plasma exposures for clobazam and its major active metabolite N-desmethylclobazam less than those in humans at the maximum recommended dose.

Chronic toxicity
In chronic toxicity studies in rats with daily oral clobazam administration of 12-1000 mg/kg, spontaneous activity was dose-dependently reduced, whereas respiratory depression and hypothermia were observed at the high dose level. Dose-dependent sedation, somnolence, ataxia and tremor were initially evident in dogs receiving daily oral doses of 2.5-80 mg/kg clobazam, which almost completely reversed in the course of the study. Similar dose-dependent effects were noted in monkeys after daily oral administration of 2.5-20 mg/kg.

Impairment of fertility
A study in rats in which clobazam was orally administered to male and female rats prior to and during mating and continuing in females to gestation day 6 had no effect on fertility and early embryonic development. The study was limited as the highest dose was associated with plasma exposures for clobazam and N-desmethylclobazam less than those in humans at the maximum recommended dose.

Genotoxicity and carcinogenicity
Clobazam is not genotoxic or tumorigenic. Follicular cell adenoma were significantly increased in rats at the 100 mg/kg clobazam high dose. In contrast to other species (mouse, dog, monkey), clobazam is known to activate the thyroid gland in rats like other benzodiazepine-containing agents. No effects on human thyroid function were noted at clinically relevant doses (20-80 mg).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aluminium Magnesium Silicate

Citric Acid Monohydrate (E330)

Disodium Hydrogen Phosphate Dihydrate

Simethicone Emulsion

Sucralose (E955)

Polysorbate 80 (E433)

Masking Flavour (contains propylene glycol (E1520))

Raspberry Flavour 545724E (contains propylene glycol (E1520))

Xanthan Gum (E415)

Sodium Methyl parahydroxybenzoate (E219) (Preservative)

Sodium Propyl parahydroxybenzoate (E217) (Preservative)

Liquid Maltitol (E965)

Purified Water

6.2 Incompatibilities

In the absence of compatibility studies, this product must not be mixed with other medicinal products or beverages.

6.3 Shelf life

Unopened: 3 years

After opening: 28 days

6.4 Special precautions for storage

Do not store above 25ºC. Do not refrigerate or freeze.

6.5 Nature and contents of container

Bottle: Amber (Type III glass)
Closure: HDPE, EPE wadded, child resistant closure
Pack size: 150ml
Syringe: Polypropylene body and HDPE plunger with a capacity of 5ml
Bottle adaptor: Low Density Polyethylene. The bottle adaptor is not pre-fitted.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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UK

8 MARKETING AUTHORISATION NUMBER(S)

PL00427/0228

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/02/2015

10 DATE OF REVISION OF THE TEXT

02/04/2026